BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT/EP00/05672

The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

EPO - DG 1

- 2. 08. 2000

(51)

REC'D 13 SEP 2000
WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears a correction, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

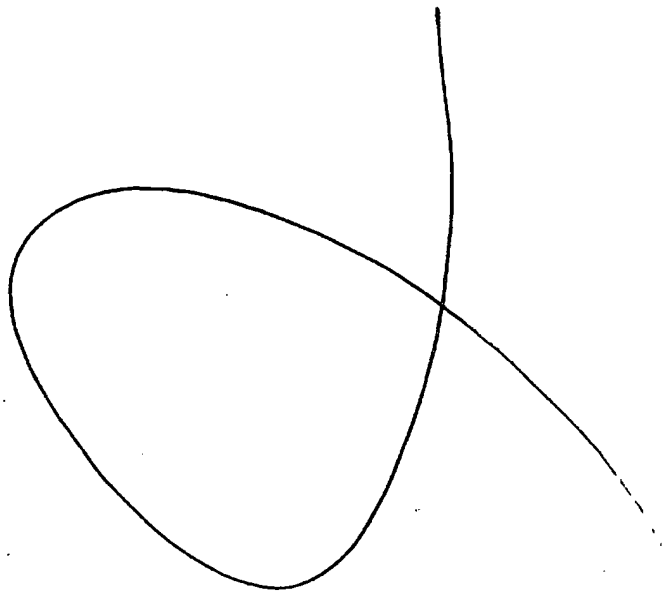
In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed A M Brewer

Dated 12 July 2000



Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

18 JUN 1999

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

THE PATENT OFFICE L 18 JUN 1999 LONDON

1. Your reference — KR/JW/P32330

2. Patent application number
(The Patent Office will fill in his part) — **9914371.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

~~SmithKline Beecham plc~~
~~New Horizons Court, Brentford, Middx TW8 9EP,~~
~~Great Britain~~

Cf. 25/6/99 F11/77

SmithKline Beecham SpA
Via Zambeletti, 20021 Baranzate di Bollate,
Milan. ITALY

Patents ADP number *(if you know it)* 06892418001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)* 5800974003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	29
Claim(s)	5
Abstract	1
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 18-Jun-99

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
f) For details of the fee and ways to pay please contact the Patent Office.

P32330

NOVEL COMPOUNDS

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

Diseases associated with loss of bone mass are known to be caused by over activity of osteoclast cells. It is also known that certain compounds, usually related to bafilomycin, are useful for treating such diseases. For example International Application Publication Number WO 91/06296 discloses certain bafilomycin macrolides for the treatment of bone affecting diseases.

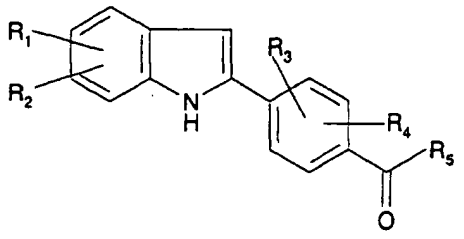
However, bafilomycin derivatives are not selective for osteoclasts in humans. The use of these compounds is therefore associated with unacceptable toxicity due to generalised blockade of other essential v-ATPases. Indeed, to date there is no known treatment which is selective for the human osteoclasts.

The search for a successful treatment for diseases associated with loss of bone mass in humans is further complicated in that the nature of the therapeutic target for the selective inhibition of the osteoclasts is controversial. Thus Baron *et al.* (International Application Publication Number WO93/01280) indicate that a specific vacuolar ATPase (V-ATPase) has been identified in osteoclasts as a potential therapeutic target. However, the Baron work was carried out in chickens and Hall *et al.* (*Bone and Mineral* **27**, 159-166, (1994)), in a study relating to mammals, conclude that in contrast to avian osteoclast V-ATPase, mammalian osteoclast V-ATPase is pharmacologically similar to the v-ATPase in other cells and, therefore, it is unlikely to be a good therapeutic target.

It has now surprisingly been found that particular indole compounds are selective for mammalian osteoclasts, acting to selectively inhibit their bone resorbing activity. These compounds are therefore considered to be particularly useful for the treatment and/or prophylaxis of diseases associated with loss of bone mass, such as osteoporosis and related osteopenic diseases, Paget's disease, hyperparathyroidism and related diseases. These compounds are also considered to possess anti-tumour activity, antiviral activity (for example against *Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A* and *B, HIV* viruses), antiulcer activity (for example the compounds may be useful for the treatment of chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), immunosupressant activity, antilipidemic activity, antiatherosclerotic activity and to be useful for the treatment of AIDS and Alzheimer's disease. Furthermore, these compounds are also considered useful in inhibiting angiogenesis i.e. the formation of new blood vessels which is observed in various types of pathological

conditions (*angiogenic diseases*) such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

Accordingly, the invention provides a compound of formula (I)



(I)

or a salt thereof, or a solvate thereof, wherein;

R_1 and R_2 each independently represents methoxy or chloro;

R_3 and R_4 each independently represents hydrogen or alkoxy, and;

R_5 represents $-NR_sR_t$ wherein R_s and R_t each independently represent hydrogen, unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

Suitable positions for substitution for R_1 or R_2 are the 4, 5, 6 or 7 position, favourably the 5 or 6 position.

In a preferred aspect R_1 is 5-chloro, and R_2 is 6-chloro.

Examples of R_3 are methoxy and ethoxy.

Suitably R_3 is located meta to the $-COR_5$ moiety.

Examples of R_4 are hydrogen and methoxy.

Suitably R_4 is located meta to the $-COR_5$ moiety.

Suitably, R_s or R_t represent unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

When R_s or R_t represent unsubstituted or substituted alkyl, suitable alkyl groups are C_{1-6} alkyl groups, for example C_1, C_2, C_3, C_4 and C_5 alkyl groups, favourably ethyl, propyl or butyl.

When R_s or R_t represent substituted alkyl, favoured groups are 3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl, and 3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl groups.

In a favoured aspect, R_s represents an unsubstituted or substituted piperidinyl group, especially a 4-piperidinyl group.

Substituents for the piperidinyl ring include alkyl, fused cycloalkyl, arylalkyl, hydroxyalkyl and polyhydroxyalkyl.

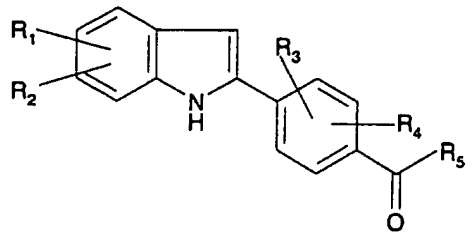
Favoured substituents for piperidinyl groups are alkyl groups.

When the piperidinyl group is substituted it is preferred that the substituents are attached to one or both of the carbon atoms alpha to the nitrogen atom.

Examples of substituted piperidinyl groups are 1,2,2,6,6-pentamethylpiperidin-4-yl and 2,2,6,6-tetramethylpiperidin-4-yl groups.

Favourably, R_t is hydrogen.

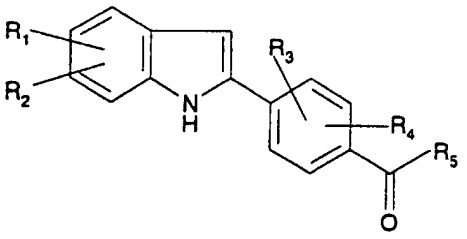
There is a subgroup of compounds within formula (I) of formula (IA)



(IA)

wherein R1, R2, R3, R4, and R5 are as defined in formula (I), Rs is 3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl or 3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl, and Rt is hydrogen.

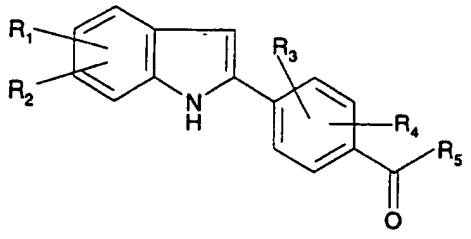
There is also a subgroup of compounds within formula (I) of formula (IB)



(IB)

wherein R1, R2, R3, R4, and R5 are as defined in formula (I), Rs is 3-pyridyl or 3-(6-methoxy)pyridyl, and Rt is hydrogen.

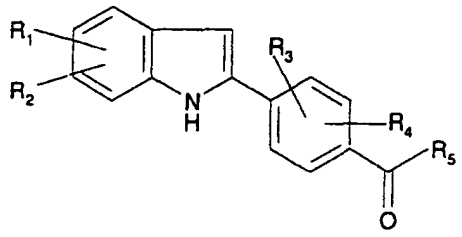
There is also a subgroup of compounds within formula (I) of formula (IC)



(IC)

wherein R2, R4, and R5 are as defined in formula (I), Rs is 2,2,6,6-tetramethylpiperidin-4-yl, Rt is hydrogen, R3 is 3-methoxy, and R1 is 5-chloro or 5-methoxy.

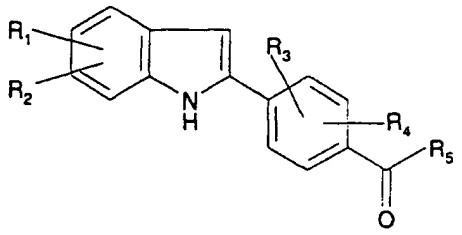
There is also a subgroup of compounds within formula (I) of formula (ID)



(ID)

wherein R1, R2, R4, and R5 are as defined in formula (I), Rs is 2,2,6,6-tetramethylpiperidin-4-yl, Rt is hydrogen, and R3 is 2-methoxy.

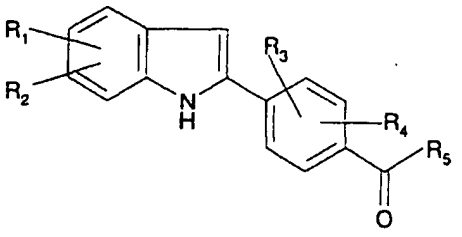
There is also a subgroup of compound within formula (I) of formula (IE)



(IE)

wherein R1, R2, R4, and R5 are as defined in formula (I), Rs is 1,2,2,6,6-pentamethylpiperidin-4-yl, Rt is hydrogen, and R3 is 2-methoxy, 3-methoxy, or 3-ethoxy.

There is also a subgroup of compounds within formula (I) of formula (IF)



(IF)

wherein R1, R2, R3, R4, and R5 are as defined in formula (I), Rs is 1-benzylpiperidin-4-yl, and Rt is hydrogen.

As used herein, the term "alkyl" includes straight or branched chain alkyl groups having from 1 to 12 , suitably 1 to 6, preferably 1 to 4, carbon atoms, such as methyl, ethyl, n- and iso-propyl and n- iso-, tert-butyl and pentyl groups, and also includes such alkyl groups when forming part of other groups such as alkoxy or alkanoyl groups.

As used herein, the term "aryl" includes phenyl and naphthyl, especially phenyl.

Suitable optional substituents for any aryl group include up to 5 substituents, suitably up to 3 substituents, selected from alkyl, alkoxy, thioalkyl, hydroxy, halo, trifluoromethyl, alkylcarbonyl, cyano, nitro, or a group $-NR_uR_v$ wherein R_u and R_v each independently represent hydrogen, alkyl or alkylcarbonyl.

Suitable arylalkyl groups include aryl C_{1-3}alkyl groups such as phenylethyl and benzyl groups, especially benzyl.

Preferably, substituted aralkyl groups are substituted in the aryl moiety.

As used herein, the term "heterocyclyl" includes saturated or unsaturated single or fused ring heterocyclic groups, each ring having 4 to 11 ring atoms, especially 5 to 8, preferably 5, 6 or 7 which ring atoms include 1, 2 or 3 heteroatoms selected from O, S, or N.

Suitable optional substituents for any heterocyclyl group includes those mentioned herein with respect to the aryl group.

As used herein, the term "halogen" or "halo" includes fluoro, chloro, bromo and iodo, suitably fluoro and chloro, favourably chloro.

When used herein "acyl" includes alkyl carbonyl.

Certain of the carbon atoms of the compounds of formula (I) are chiral carbon atoms and may therefore provide stereoisomers of the compound of formula (I). The invention extends to all stereoisomeric forms of the compounds of formula (I) including enantiomers and mixtures thereof, including racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include acid addition salts and salts of carboxy groups.

Suitable pharmaceutically acceptable acid addition salts include salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such, for example as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic

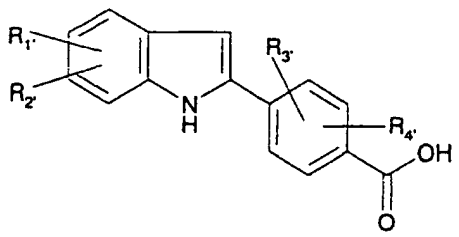
acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid or acetylsalicylic acid.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium and lithium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with C1-6alkylamines such as triethylamine, hydroxyC1-6alkylamines such as 2-hydroxyethylamine, bis-(2- hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as dicyclohexylamine, or with procaine, 1,4-dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

Suitable solvates of the compounds of the formula (I) are pharmaceutically acceptable solvates, such as hydrates.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

A compound of formula (I) may be prepared by amidation of a suitable carboxylic acid with a suitable amine. Accordingly, the present invention also provides a process for the preparation of a compound of formula (I) or a salt thereof or a solvate thereof, which process comprises the amidation of a compound of formula (II)



(II)

wherein R_1', R_2', R_3', and R_4' each respectively represent R_1, R_2, R_3, and R_4 as defined in relation to formula (I) or a protected form thereof, with a compound of formula (III)

$$HNR_5'R_t' \qquad \text{(III)}$$

wherein R_S' and R_t' each represent R_S and R_t as defined in relation to formula (I) or a protected form thereof and thereafter, as necessary, carrying out one or more of the following steps:

(i) converting one compound of formula (I) into another compound of formula (I);

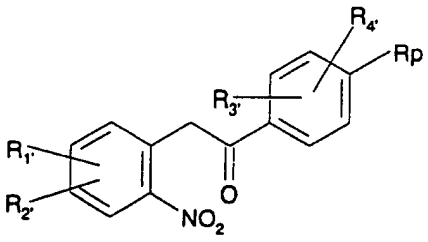
(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

Suitable amidation methods include treating the compound of formula (II) with a compound of formula (III).

The reaction between the compounds of formula (II) and (III) may be carried out under the appropriate conventional amidation conditions, for example in an aprotic solvent such as dimethylformamide, acetonitrile and tetrahydrofuran, at any temperature providing a suitable rate of formation of the required product, conveniently at ambient temperature; preferably the amidation reaction is carried out in the presence of a peptide coupling reagent such as 1-hydroxybenzotriazole (HOBT), and/or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC).

A compound of formula (II) may be prepared by cyclising a compound of formula (IV):



(IV)

wherein R_1', R_2', R_3', and R_4' are as defined in relation to formula (II) and R_p represents a protected carboxyl group or a group convertible into a carboxyl group and thereafter, as required, converting the group R_p into a carboxyl group.

Suitably, the cyclisation reaction is carried out under reductive cyclisation conditions, for example by using powdered iron/acetic acid mixtures or an alkali metal hydrogensulphite, such as sodium hydrogensulphite, in any suitable solvent such as tetrahydrofuran, ethanol, methanol or water or mixtures thereof at any temperature providing a suitable rate of formation of the required product, such as an elevated temperature, conveniently at the reflux temperature of the solvent.

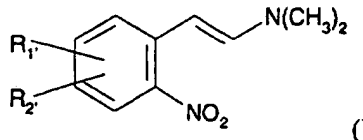
When Rp is a protecting group, suitable protecting groups include lower alkyl groups, for example methyl or ethyl groups, which may be removed by

conventional hydrolysis methods, for example by use of basic hydrolysis using ethanolic potassium hydroxide.

When Rp is a group convertible into a carboxyl group, suitable groups include cyano group. Such groups may be converted into carboxyl groups using conventional methods for example when R_p is a cyano group it may be converted into a carboxyl group by hydrolysis using conventional methods, for example by use of basic hydrolysis using potassium hydroxide solution in ethanol at reflux.

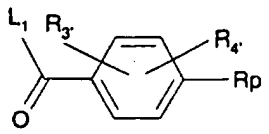
A preferred value of Rp is a cyano group.

A compound of formula (IV) is prepared by reacting a compound of formula (V)



(V)

wherein R_1' and R_2' are as defined in relation to formula (II) with a compound of formula (VI)

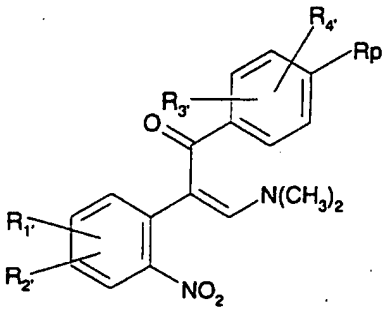


(VI)

wherein R_3', R_4', and Rp are as defined in relation to formula (IV) and L_1 represents a leaving group, such as a halogen group, for example a chloro group.

The reaction between the compounds of formula (V) and (VI) may be carried out in an inert hydrocarbon solvent, such as cyclohexane, at any temperature providing a suitable rate of formation of the required product, preferably at an elevated temperature, such as the reflux temperature of the solvent and in presence of a base, preferably a tertiary amine such as triethylamine.

The reaction between the compounds of formulae (V) and (VI) proceeds via an intermediate which is not usually isolated and which provides the required compound of formula (IV) on heating in situ. It an alternative aspect, the intermediate is isolated thereby providing an alternative preparation of the compound of formula (IV) wherein the compound of formula (VII)



(VII)

wherein R_1', R_2', R_3', and R_4' are as defined in relation to formula (II) and Rp is as defined in relation to formula (IV), is heated to provide the compound of formula (IV) as hereinbefore defined.

The conversion of compound (VII) into the compound of formula (IV) is conveniently carried out in a polar solvent mixture, such as dioxane and water, usually at the reflux temperature of the solvent mixture in conditions analogous to those described in *J. Het. Chem.* **11**, 219-221, (1974).

The compounds of formula (V) are known compounds or they are prepared using methods analogous to those used to prepare known compounds, such as those disclosed by Meervein *et al Ann. Chem.* 641, 1 (1961) and Org. Synth. Collective VII, 34-41.

The compounds of formula (III) are known or they are prepared using methods analogous to those used to prepare known compounds, such as those described in J. March, *Advanced Organic Chemistry*, 3rd Edition (1985), Wiley Interscience.

Amines of general formula HNRsRt' may be prepared using the methods known in the art for the preparation of amines, for example as taught in *Houben-Weil, Methoden der Organischen Chemie*, Vol. XI/1 (1957) and Vol. E16d/2 (1992), Georg Thieme Verlag, Stuttgart.

A compound of formula (I) or a salt thereof or a solvate thereof may be isolated from the above mentioned processes according to standard chemical procedures.

The preparation of salts and/or solvates of the compounds of formula (I) may be performed using the appropriate conventional procedure.

If required mixtures of isomers of the compounds of the invention may be separated into individual stereoisomers and diastereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Suitable optically active acids which may be used as resolving agents are described in "*Topics in Stereochemistry*", Vol. 6, Wiley Interscience, 1971, Allinger, N.L. and Eliel, W.L. Eds.

Alternatively, any enantiomer of a compound of the invention may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

The absolute configuration of compounds may be determined by conventional methods such as X-ray crystallographic techniques.

The protection of any reactive group may be carried out at any appropriate stage in the aforementioned processes. Suitable protecting groups include those used conventionally in the art for the particular group being protected. Protecting groups may be prepared and removed using the appropriate conventional procedure, for example OH groups, including diols, may be protected as the silylated derivatives by treatment with an appropriate silylating agent such as di-tert-butylsilylbis(trifluoromethanesulfonate). The silyl group may then be removed using conventional procedures such as treatment with hydrogen fluoride, preferably in the form of a pyridine complex and optionally in the presence of alumina, or by treatment with acetyl chloride in methanol. Alternatively benzyloxy groups may be used to protect phenolic groups, the benzyloxy group may be removed using catalytic hydrogenolysis using such catalysts as palladium (II) chloride or 10% palladium on carbon.

Amino groups may be protected using any conventional protecting group, for example tert-butyl esters of carbamic acid may be formed by treating the amino group with di-tert-butyldicarbonate, the amino group being regenerated by hydrolysing the ester under acidic conditions, using for example hydrogen chloride in aqueous ethanol or trifluoroacetic acid in methylene dichloride. An amino group may be protected as a benzyl derivative, prepared from the appropriate amine and a benzyl halide under basic conditions, the benzyl group being removed by catalytic hydrogenolysis, using for example a palladium on carbon catalyst.

Indole NH groups and the like may be protected using any conventional group, for example benzenesulphonyl, methylsulphonyl, tosyl, formyl, acetyl (all of them removable by treatment with alkaline reagents), benzyl (removable either with sodium in liquid ammonia or with $AlCl_3$ in toluene), allyl (removable by treatment with rhodium (III) chloride under acidic conditions), benzyloxycarbonyl (removable either by catalytic hydrogenation or by alkaline treatment), trifluoroacetyl (removable by either alkaline or acidic treatment), t-butyldimethyl-silyl (removable by treatment with tetrabutylammonium fluoride), 2-(trimethylsilyl)ethoxymethyl (SEM) (removable by treatment with tetrabutylammonium fluoride in the presence of ethylendiamine), methoxymethyl (MOM) or methoxyethyl (MEM) groups (removed by mild acidic treatment).

Carboxyl groups may be protected as alkyl esters, for example methyl esters, which esters may be prepared and removed using conventional procedures,

one convenient method for converting carbomethoxy to carboxyl is to use aqueous lithium hydroxide.

A leaving group is any group that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable examples of such groups unless otherwise specified are halogen groups, mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

The salts, esters, amides and solvates of the compounds mentioned herein may as required be produced by methods conventional in the art. For example, acid addition salts may be prepared by treating a compound of formula (I) with the appropriate acid.

Esters of carboxylic acids may be prepared by conventional esterification procedures, for example alkyl esters may be prepared by treating the required carboxylic acid with the appropriate alkanol, generally under acidic conditions.

Amides may be prepared using conventional amidation procedures, for example amides of formula $CONR_S'R_t'$ may be prepared by treating the relevant carboxylic acid with an amine of formula $HNR_S'R_t'$ wherein R_S' and R_t' are as defined above. Alternatively, a C_{1-6} alkyl ester such as a methyl ester of the acid may be treated with an amine of the above defined formula $HNR_S'R_t'$ to provide the required amide, optionally in presence of trimethylalluminium following the procedure described in *Tetrahedron Lett.* **48**, 4171-4173, (1977).

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties.

The present invention therefore provides a method for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals which method comprises the administration of an effective non-toxic amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.

In a further aspect, the present invention provides a method for the treatment of osteoporosis and related osteopenic diseases in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

In a further aspect, the present invention also provides a method for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by Helicobacter pylori), autoimmune diseases and transplantation, for the treatment

and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal. which comprises administering an effective, non-toxic, amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

In a still further aspect, the present invention a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for use in the treatment or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for use in the treatment of or prophylaxis of osteoporosis and related osteopenic diseases.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for use in the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal.

Of particular interest is the osteoporosis associated with the peri and post menopausal conditions. Also encompassed are the treatment and prophylaxis of Paget's disease, hypercalcemia associated with bone neoplasms and all the types of osteoporotic diseases as classified below according to their etiology:

Primary osteoporosis
Involutional
Type I or postmenopausal
Type II or senile
Juvenile
Idiopathic in young adults

Secondary osteoporosis
Endocrine abnormality
Hyperthyroidism
Hypogonadism
Ovarian agenesis or Turner's syndrome
Hyperadrenocorticism or Cushing's syndrome
Hyperparathyroidism
Bone marrow abnormalities
Multiple myeloma and related disorders
Systemic mastocytosis
Disseminated carcinoma
Gaucher's disease
Connective tissue abnormalities
Osteogenesis imperfecta
Homocystinuria
Ehlers-Danlos syndrome
Marfan's syndrome
Menke's syndrome
Miscellaneous causes
Immobilisation or weightlessness
Sudeck's atrophy
Chronic obstructive pulmonary disease
Chronic alcoholism
Chronic heparin administration
Chronic ingestion of anticonvulsant drugs

In addition the invention encompasses the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving *Semliki Forest* virus, *Vesicular Stomatitis* virus, *Newcastle Disease* virus, *Influenza A* and *B* viruses, *HIV* virus), ulcers (for example chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), for use as immunosupressant agents in autoimmune diseases and transplantation, antilipidemic agents for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases and to be useful for the treatment of AIDS and Alzheimer's disease. These compounds are also considered useful in treating angiogenic diseases, i.e. those pathological conditions which are dependent on angiogenesis, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

A compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier therefor.

Active compounds or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof are normally administered in unit dosage form.

An amount effective to treat the disorders hereinbefore described depends upon such factors as the efficacy of the active compounds , the particular nature of the pharmaceutically acceptable salt or pharmaceutically acceptable solvate chosen, the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.01 to 50 mg, for example 1 to 25 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 3 or 2 to 4 times a day such that the total daily dose is normally in the range, for a 70 kg adult of 0.01 to 250 mg, more usually 1 to 100 mg, for example 5 to 70 mg, that is in the range of approximately 0.0001 to 3.5 mg/kg/day, more usually 0.01 to 1.5 mg/kg/day, for example 0.05 to 0.7 mg/kg/day.

In such treatments the active compound may be administered by any suitable route, e.g. by the oral, parenteral or topical routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a human or veterinary pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents,

tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

For topical administration, the composition may be in the form of a transdermal ointment or patch for systemic delivery of the active compound and

may be prepared in a conventional manner, for example, as described in the standard textbooks such as 'Dermatological Formulations' - B.W. Barry (Drugs and the Pharmaceutical Sciences - Dekker) or Harrys Cosmeticology (Leonard Hill Books).

Accordingly, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of osteoporosis and related osteopenic diseases.

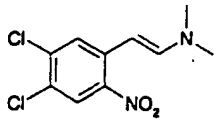
In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia., viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours,.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention. As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The following, descriptions, examples and pharmacological methods illustrate the invention but do not limit it in any way.

Descriptions and Examples

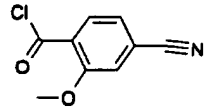
Description 1: ***trans*-4,5-Dichloro-2-nitro-β-dimethylaminostyrene**



A solution of 10.3 g (50 mmol) of 4,5-dichloro-2-nitrotoluene (*Helv. Chim. Acta* **1936**, *19*, 434-439) in a mixture of 11.9 g (100 mmol) *N,N*- dimethylformamide

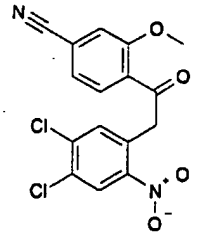
dimethylacetal in DMF (25 ml) was heated at 100°C for 16 h. The dark reaction mixture was concentrated *in vacuo*, the residue diluted with methylene chloride and washed twice with water. The organic solution was dried over $MgSO_4$, concentrated *in vacuo* affording 12.6 g (48 mmol, yield 96.5%) of the title compound as dark red crude crystals.

Description 2: **2-Methoxy-4-cyanobenzoyl chloride**



2-Methoxy-4-cyanobenzoic acid (*Tetrahedron Letters*, **1986**, *27*(49), 5997-6000) (1 g, 5.6 mmol) was dissolved in CH_2Cl_2 (20 ml). Oxalyl chloride (1.5 ml, 8.2 mmol) was rapidly introduced into the solution and a drop of DMF was added. A vigorous reaction took place with the abundant evolution of gaseous products. The solution was stirred for 1 h then allowed to stand over night. Solvent was removed using a rotary evaporator to leave 1.1 g of an off white solid (5.6 mmol, yield 99%) that was used without further purification.

Description 3: **3-Methoxy-4-[2-[(4,5-dichloro-2-nitro)phenyl]-1-oxo-ethyl]-benzonitrile**

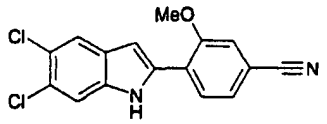


2-Methoxy-4-cyanobenzoyl chloride (1.1 g, 5.6 mmol), prepared as in Description 3, was added portionwise to a stirred solution of *trans*-4,5-dichloro-2-nitro-β-dimethylaminostyrene (1.47 g, 5.6 mmol) and triethylamine (1.5 ml, 10 mmol) in cyclohexane (20 ml). The solution was then refluxed for 16 h. The reaction was cooled and all the volatile products removed using a rotary evaporator. A dark residue was obtained which was then dissolved in CH_2Cl_2 (40 ml) and washed once with 10% Na_2CO_3 solution (20 ml). The organic layer was then dried with anhydrous Na_2SO_4, filtered and the solvent removed using a rotary evaporator. Dark brown to black powder (2.42 g) was obtained that was dissolved in as little ethyl acetate as possible and hexane was added to this solution to precipitate light brown powder (1.72 g, mp= 167-170°C) that was used without further purification in the next step.

This crude intermediate (1.2 g) was dissolved in 1,4-dioxane (20 ml) and water (10 ml) was added. The solution was refluxed for 48 h, filtered while still hot and then chilled in an ice water bath. Yellow to brown crystals were collected on a Buchner funnel obtaining 0.60 g (1.6 mmol, yield 30%) of the title compound, mp = 171-174 °C.

^{1}H NMR ($CDCl_3$) δ = 8.27 (s, 1H); 7.81 (d,1H); 7.49 (s, 1H); 7.35 (dd, 1H); 7.28 (d, 1H); 4.61 (s, 2H); 4.00 (s, 3H).

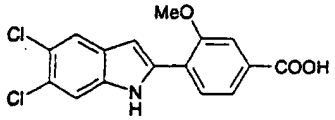
Description 4: **3-Methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzonitrile**



3-Methoxy-4-[2-(4,5-dichloro-2-nitro)phenyl-1-oxo-ethyl]-benzonitrile (0.4 g, 1.0 mmol) was dissolved in EtOH (10 ml) and AcOH (10 ml). The solution was brought to gently reflux and iron powder (0.5 g, 9 mmol) was added in small portions over the period of an hour. The solution was refluxed for 12 h after which the solvents were removed using a rotary evaporator. The residue was extracted several times with THF. After removal of the solvent, crude 3-methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzonitrile (0.35 g, 1.0 mmol, yield 100%) was obtained that was used in the next step without further purification. mp = 241-244 °C.

^{1}H NMR (DMSO-d_6) δ = 11.60 (s br, 1H); 7.98 (d, 1H); 7.85 (s, 1H); 7.67 (s, 1H); 7.65 (d, 1H); 7.55 (dd, 1H); 7.14 (s, 1H); 4.00 (s, 3H).

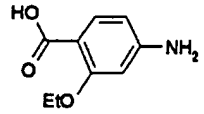
Description 5: **3-Methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid**



3-Methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzonitrile (0.35 g, 1.0 mmol) was suspended in 30 % NaOH (20 ml) and 95% EtOH (20 ml). The mixture was refluxed for 12 h and then allowed to cool to room temperature. The suspension was concentrated to about half volume using a rotary evaporator and then filtered on a Buchner funnel obtaining a tan to yellow coloured powder. This was stirred for 2 hour in 10% HCl. The solution was then filter to yield 0.256 g (0.76 mmol, yield 69%) of the crude title compound that was purified by chromatography to yield 150 mg of pure title compound, mp > 270 °C.

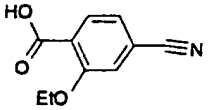
^{1}H NMR (DMSO-d_6) δ = 11.60 (broad s, 1H); 7.92 (d, 1H); 7.83 (s, 1H); 7.66 (m, 3H); 7.10 (s, 1H); 4.02 (s, 3H).

Description 6: **2-Ethoxy-4-aminobenzoic acid**



A suspension of methyl 2-ethoxy-4-acetamidobenzoate (50 g, 211 mmol) in aqueous solution of NaOH (15% W/W, 200 ml) was gently refluxed for 16 hours. The resulting pale brown solution was allowed to cool to room temperature and then further cooled in an ice water bath. Concentrated HCl (37% w/w) was added until the solution reached a pH of 6. The solid precipitated from the solution was filtered under vacuum, dried at 50°C to give 38.3 g of the title compound (yield 100%).

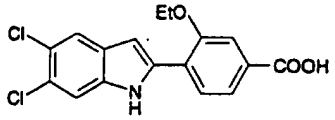
Description 7: **2-Ethoxy-4-cyanobenzoic acid**



In a 1l reactor equipped with a sealed mechanical stirrer, CuCN (12 g, 134 mmol) were suspended in 100 ml of distilled water. NaCN (18.3 g, 373 mmol) was added with vigorous stirring and the internal temperature was kept below 40°C until all the CuCN went into solution. The suspension of 2-ethoxy-4-aminobenzoic acid (20 g, 110 mmol) in water (200 ml) and concentrated HCl (33 ml) was stirred and cooled in an ice bath. When the temperature reached 5°C, a solution of $NaNO_2$ (9.7 g, 140 mmol) in water (30 ml) was added dropwise at such a rate as to maintain the temperature below 5 °C.

When all the $NaNO_2$ was added, the solution was slowly introduced through an ice cooled dropped funnel into the reactor containing the NaCN/CuCN solution. A reaction took place with the vigorous formation of N_2. A few drops of octanol were added to keep the foaming under control. Stirring was continued for 4 h. The resulting suspension was then extracted with ethyl acetate (3x100 ml) and the organic phase dried over $MgSO_4$ and evaporated under vacuum obtaining 15 g of the title compound (yield 71.1 %) as a light brown powder, mp = 170-172°C.

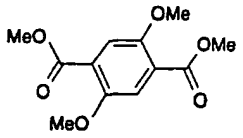
Description 8: **3-Ethoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid**



The title compound was prepared starting from 2-ethoxy-4-cyanobenzoic acid. prepared as in Description 7, following the procedure in Description 1-5. The title

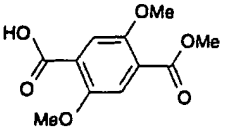
compound was prepared with an overall yield of 18 %, based on the 2-ethoxy-4-cyanobenzoic acid.

Description 9: **Dimethyl 2,5-dimethoxyterephthalate**



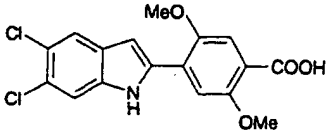
A suspension of 2,5-dihydroxyterephthalic acid (5 g, 25 mmol), K_2CO3 (10 g, 72 mmol) and dimethyl sulphate (11 ml, 116 mmol) in acetone (100 ml) was stirred and refluxed for 24. The mixture was filtered while still hot and the solvent was evaporated to about half of the original volume. On cooling white needles precipitated and were filtered and dried obtaining 4.6 g of the title compound (yield 73%), mp = 141-143°C.

Description 10: **2,5-Dimethoxyterephthalic acid monomethyl ester**



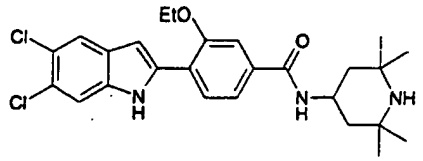
A suspension of dimethyl 2,5-dimethoxyterephthalate (4 g, 15.7 mmol), prepared as in Description 9, in methanolic KOH (0.86 g of KOH in 100 ml MeOH) was refluxed for 3 h. The solution was cooled and the solvent removed under vacuum. The residue was treated with dilute HCl and the solid filtered off. The crude mixture was purified by column chromatogrphy using 1:1 ethyl acetate/hexane as a solvent obtaining 1.72 g of the title compound (yield 44.7%), mp = 123-124°C

Description 11: **2,5-Dimethoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid**



The title compound was prepared starting from 2,5-dimethoxyterephthalic acid monomethyl ester, prepared as in Description 10, following the procedure in Description 1-5. The title compound was prepared with an overall yield of 46%, based on 2,5-dimethoxyterephthalic acid monomethyl ester

Example 1: **4-(5,6-Dichloro-1H-indol-2-yl)-3-ethoxy-N-(2,2,6,6-tetramethylpiperidin-4-yl)-benzamide.**



To a suspension of 3-ethoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid (200 mg, 0.57 mmol), prepared as in Description 8, in CH_3CN (14 ml) and THF (6 ml), WSC (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) (104 mg, 55 mmol) and 1-hydroxybenzotriazole (77 mg, 0.57 mmol) were added and the reaction was refluxed for 3h.

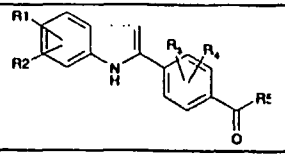
4-Amino-2,2,6,6-tetramethylpiperidine (108 mg, 0.7 mmol) were introduced into the reaction mixture and refluxing continued for another 2h. The reaction was cooled and the solvent was removed under vacuum. The residue was treated with 30 ml of 10% NaOH solution and then filtered. The resulting solid was washed with water, dried and purified by chromatography on silica gel to yield 154 mg of the title compound as light yellow powder (yield 55%), mp = 253-255 °C.

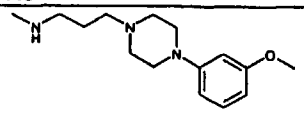
^{1}H NMR (DMSO-d_6) δ = 11.56 (s br, 1H); 8.28 (d br, 1H); 7.85 (d, 1H); 7.82 (s, 1H) 7.64 (s, 1H); 7.59 (s, 1H); 7.57 (d, 1H); 7.11 (s, 1H); 4.40-4.21 (m, 1H); 4.30 (q, 2H); 1.80 (d br, 2H); 1.50 (t, 3H); 1.30 (m, 2H); 1.28 (s, 6H); 1.15 (s, 6H).

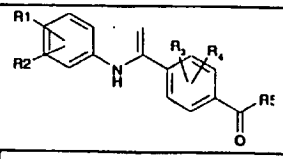
ESI POS; AQA ; solvent: MeOH / spray 3 kV / skimmer: 20 V/ probe 135°C: m/z 488 (MH^+)

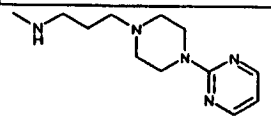
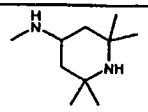
The Example compounds listed in Table 1 were prepared according to the procedure of Example 1:

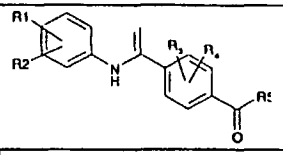
Table 1

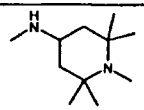
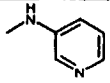
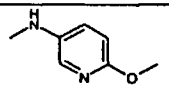
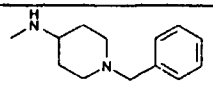


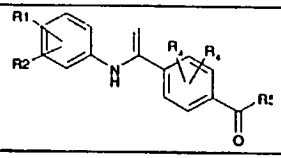
Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
2	4-(5,6-Dichloro-1H-indol-2-yl)-N-[3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl]-3-methoxybenzamide	5-Cl	6-Cl	3-OMe	-H		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V/ capillary 220°C : m/z 474 (MH^+) B) CID Offset= -56 V :m/z 567; 375; 318.	201-205	^{1}H-NMR (DMSO-d_6) δ = 11.53 (s br, 1H); 8.55 (t br, 1H); 7.88 (d, 1H); 7.81 (s, 1H); 7.66 s, 1H); 7.60 (d, 1H); 7.57 (dd, 1H); 7.10 (dd, 1H); 7.04 (m, 1H); 6.51 (dd, 1H); 6.43 (dd, 1H); 6.35 dd, 1H); 4.00 (s, 3H); 3.70 (s, 3H); 3.30 (m, 2H); 3.13 (m, 4H); 2.58 (m, 4H); 2.41 (t, 2H); 1.80-1.72 (m, 2H).

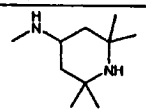
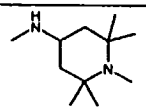
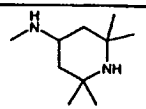


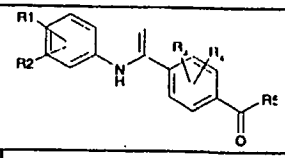
Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
3	4-(5,6-Dichloro-1H-indol-2-yl)-N-[3-[4-(2-pyrimidyl)piperazin-1-yl]propyl]-3-methoxybenzamide	5-Cl	6-Cl	3-OMe	-H		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V/ capillary 220°C : m/z 539 (MH^+) B) CID Offset= -56 V : m/z 539; 575; 318.	234-237	^{1}H-NMR (DMSO-d_6 at 343 K) δ = 11.30 (s br, 1H); 8.32 (d, 2H); 8.31 (t br, 1H); 7.85 (d, 1H); 7.79 (s, 1H); 7.68 (s, 1H); 7.60 s br, 1H); 7.56 (d, 1H); 7.01 (s br, 1H); 6.59 (t, 1H); 4.02 (s, 3H); 3.7 7(m, 4H); 3.40 (dt, 2H); 2.50-2.40 (m, 6H); 1.87-1.73 (m, 2H).
4	4-(5,6-Dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide	5-Cl	6-Cl	3-OMe	-H		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V/ capillary 220°C : m/z 474 (MH^+) B) CID Offset= -56 V : m/z 474; 457; 401; 318; 290; 123; 58.	151-156	^{1}H-NMR (DMSO-d_6) δ = 11.30 (s br, 1H); 7.95 (d br, 1H); 7.82 (d, 1H); 7.77(s, 1H); 7.68 (s, 1H); 7.61 (d, 1H); 7.56 (dd, 1H); 7.01 (d, 1H); 4.45-4.30 (m, 1H); 4.01 (s, 3H); 1.80 (m, 2H); 1.30 (m, 2H); 1.30 (s, 6H); 1.15 (s, 6H).

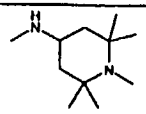


Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
5	4-(5,6-Dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-ethoxybenzamide	5-Cl	6-Cl	3-OEt	-H		ESI POS; AQA; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: m/z 502 (MH^+)	> 250	^{1}H-NMR (DMSO-d_6) δ = 11.5 5(s br, 1H); 8.22 (d br, 1H); 7.85 (d, 1H); 7.82 (s, 1H); 7.63 (s, 1H); 7.58 (s, 1H); 7.57 (d, 1H); 7.10 (s br, 1H);4.29 (q, 2H); 4.29-4.14 (m, 1H); 2.22 (s, 3H); 1.75 (dd, 2H); 1.50 (t, 2H); 1.49 (t, 3H); 1.12 (s, 6H); 1.08 (s, 6H).
6	4-(5,6-Dichloro-1H-indol-2-yl)-N-(3-pyridyl)-3-ethoxybenzamide	5-Cl	6-Cl	3-OEt	-H			237-239	
7	4-(5,6-Dichloro-1H-indol-2-yl)-N-(3-(6-methoxypyridyl))-3-ethoxybenzamide	5-Cl	6-Cl	3-OEt	-H			258-260	
8	4-(5,6-Dichloro-1H-indol-2-yl)-N-(1-benzylpiperidin-4-yl)-3-ethoxybenzamide hydrochloride	5-Cl	6-Cl	3-OEt	-H			295	



Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
9	4-(5,6-Dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-2,5-dimethoxybenzamide	5-Cl	6-Cl	2-OMe	5-OMe		A) EI; TSQ 700;400 mA; 70 V: m/z 567 (MH^+) B) ESI POS; AQA; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: m/z 504 (MH^+)	148-152	^{1}H-NMR (DMSO-d_6) δ = 11.60 (s br, 1H); 7.95 (d br, 1H); 7.82 (s, 1H); 7.69 (s, 1H); 7.52 (s, 2H); 7.13 (s br, 1H); 4.40-4.21 (m, 1H); 4.00 (s, 3H); 3.92 (s, 3H); 1.78 (dd, 2H); 1.20 (s, 6H); 1.12 (dd, 2H); 1.06 (s, 6H).
10	4-(5,6-Dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,5-dimethoxybenzamide	5-Cl	6-Cl	2-OMe	5-OMe		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V/ capillary 220°C: m/z 518 (MH+) B) ESI DAU +518 (Collision gas: Argon): m/z 518; 487; 431; 365; 348; 123.	143-147	^{1}H-NMR (DMSO-d_6) δ = 11.58 (s br, 1H); 7.95 (d br, 1H); 7.81 (s, 1H); 7.68 (s, 1H); 7.51 (s, 2H); 7.13 (s br, 1H); 4.28-4.10 (m, 1H); 3.95 (s, 3H); 3.90 (s, 3H); 2.20 (s, 3H); 1.78 (dd, 2H); 1.39 (dd, 2H); 1.10 (s, 6H); 1.06 (s, 6H).
11	4-(5-Methoxy-6-chloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide	5-OMe	6-Cl	3-OMe	-H				



Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
12	4-(5-Methoxy-6-chloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-methoxybenzamide	5-OMe	6-Cl	3-OMe	-H				

Biological Assays

Background. It is known that, upon attachment to bone, an electrogenic H^+ - adenosine triphosphatase (ATPase) is polarised to the osteoclast-bone interface. The pump transports massive quantities of protons into the resorption microenvironment to effect mobilisation of the bone mineral and to create the acidic pH required by collagenases to degrade the bone matrix.

The vacuolar nature of the osteoclast proton pump was originally recognised by Blair [H. C. Blair at al., *Science*, **245**, 855 (1989)] and than confirmed by Bekker [P.J. Bekker et al., *J. Bone Min. Res.*, **5**, 569 (1990)] and Väänänen [H.K. Väänänen et al., *J. Cell. Biol.*, **111**, 1305 (1990)]. Evidence was based upon preparations of ruffled membrane fragments from avian osteoclasts (obtained from the medullar bone of calcium-starved egg-laying hens). The resulting membrane vesicles acidify in response to ATP, which is easily assessed by measuring the fluorescence quench of acridine orange, a weak base which accumulates into acidic compartments.

The biochemical pattern indicated that the osteoclast proton pump belonged to the vacuolar-like ATPases since proton transport was inhibited by N-ethylmaleimide (NEM), a sulphydryl reagent, and by bafilomycin A_1, a selective inhibitor of vacuolar H^+ -ATPases [J.E. Bowman et al., *Proc. Natl. Acad. Sci. USA*, **85**, 7972 (1988)], whilst it was not inhibited by ouabain, an inhibitor of Na^+/K^+-ATPases; sodium orthovanadate, an inhibitor of P-ATPases, or by omeprazole or SCH 28080, both of which are inhibitors of gastric H^+/K^+-ATPase [J.P. Mattsson et al., *Acta Physiol. Scand.*, **146**, 253 (1992)].

It is known that specific inhibitors of vacuolar ATPases, such as bafilomycin A_1, are able to inhibit bone resorption in osteoclast cultures [K. Sundquist *et al.*, *Biochem. Biophys. Res. Commun.* **168**, 309-313 (1990)]

Inhibition of Proton Transport and v-ATPase Activity in Membrane Vesicles.

Preparation of crude bone microsomes from calcium-starved egg-laying hens. Vesicles were prepared from medullar bone obtained from tibiae and femurs of egg-laying hens which were calcium-starved for at least 15 days. Briefly, bone fragments were scraped with a 24 scalpel blade, suspended in 40 ml of isolation medium (0.2 M sucrose, 50 mM KCl, 10 mM Hepes, 1 mM EGTA, 2 mM dithiotheitrol, pH 7.4) and filtered through a 100 µm pore size nylon mesh. The whole procedure was performed at 4°C. After homogenisation in a potter (20 strokes) in 40 ml of isolation medium an initial centrifugation (6,500 x g_{max} x 20 min) was performed to remove mitochondria and lysosomes. The supernatant was centrifuged at 100,000 x g_{max} for 1 hr and the pellet was collected in 1 ml of isolation medium, divided into 200 µl

aliquots, immediately frozen in liquid nitrogen and stored at -80°C. The protein content was determined using a Biorad colourimetric kit according to Bradford [M. Bradford, *Anal. Biochem.*, 72, 248 (1976)]. For the proton transport assay, 5-10 µl of membranes were used.

Purification of osteoclast membranes. 1 ml of crude microsomal vesicles prepared above were applied (about 0.2 ml per tube) on the top of a sucrose step-gradient consisting of 3.5 ml of 15%, 30% and 45 % (w/w) sucrose in isolation medium and centrifuged at 280,000 g_{max} for 2 h (SW 41 Ti rotor). After centrifugation the 30-45% sucrose interfaces were collected, diluted approx. 20-fold in isolation medium and pelletted at 100,000 g_{max} for 1 hour (SW 28 rotor). The pellet was then resuspended in 1 ml of isolation medium, aliquoted and frozen in liquid N_2 and stored at -80°C until used.

Human kidney membranes were obtained from the cortex of a human kidney, frozen immediately after surgery, according to the method reported in the literature for bovine kidney (S. Gluck, *J. Biol. Chem.*, **265**, 21957 (1990)).

Preparation of human osteoclast microsomal vesicles. Osteoclast-like giant cells isolated from osteoclastoma tumor were homogenized with a glass-teflon homogenizer (1000 rpm x 20 strokes), and the material was centrifuged at 6000 x gmax for 20 minutes. The resulting pellet was then spun at 100000 x gmax for 60 minutes to pellet the microsomal fraction. Resuspended in 1 ml of isolation medium pH 7.4, frozen by liquid nitrogen immersion and stored at -80°C until used.

Proton transport in membrane vesicles was assessed, semi-quantitatively, by measuring the initial slope of fluorescence quench of acridine orange (excitation 490 nm; emission 530 nm) after addition of 5-20 µl of membrane vesicles in 1 ml of buffer containing 0.2 M sucrose, 50 mM KCl, 10 mM Hepes pH 7.4, 1 mM ATP.Na2, 1 mM CDTA, 5 µM valinomycin and 4 µM acridine orange. The reaction was started by addition of 5 mM MgSO4. Results were expressed as the percent of the mean of two controls.

Inhibition of bafilomycin-sensitive ATPase activity was assessed in purified membrane vesicles by measuring the release of inorganic phosphate (Pi) during 30 min of incubation at 37°C in a 96-well plate either in the presence or in the absence of bafilomycin A1. The reaction medium contained 1 mM ATP, 10 mM HEPES-Tris pH 8, 50 mM KCl, 5 uM valinomycin, 5 uM nigericin, 1 mM CDTA-Tris, 100 uM ammonium molybdate, 0.2 M sucrose and membranes (20 ug protein/ml). The reaction was initiated by $MgSO_4$ (8-arm pipette) and stopped, after 30 min, by addition of 4 volumes of the malachite green reagent (96-arm pipette) prepared according to Chan [*Anal. Biochem.* **157**, 375 (1986)]. Absorbance at 650 nm was

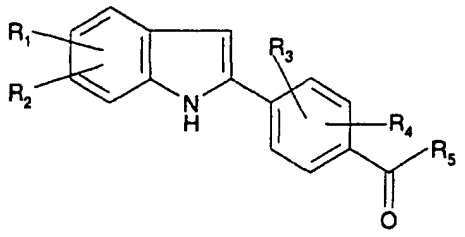
measured after 2 min using a microplate reader. Results are expressed as nmol (Pi) × mg protein^{-1}×min^{-1} and, for each experiment, represent the mean±sem of triplicates.

Pharmacological Data

Compounds described in the present invention are able to inhibit bafilomycin-sensitive ATPase of chicken osteoclast in a range from 50 nM to 2μM and of human osteoclast in a range from 30 nM to 5 μM.

Claims:

1. A compound of formula (I)



(I)

or a salt thereof, or a solvate thereof, wherein;

R_1 and R_2 each independently represents methoxy or chloro;

R_3 and R_4 each independently represents hydrogen or alkoxy, and;

R_5 represents $-NR_sR_t$ wherein R_s and R_t each independently represent hydrogen, unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

2. A compound according to claim 1 wherein R_1 and R_2 each independently represents chloro.

3. A compound according to claim 2 wherein R_1 is 5-chloro and R_2 is 6-chloro.

4. A compound according to any one claims 1 to 3 wherein R_s or R_t represents unsubstituted or substituted alkyl or unsubstituted or substituted heterocyclyl.

5. A compound according to claim 4 wherein R_s or R_t represent unsubstituted or substituted C_{1-6} alkyl groups.

6. A compound according to claim 4 wherein R_s or R_t represent 3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl or 3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl groups.

7. A compound according to claim 4 wherein R_s represents an optionally substituted piperidinyl group.

8. A compound according to claim 7 wherein R_5 represents a 1,2,2,6,6-pentamethylpiperidin-4-yl group or a 2,2,6,6-tetramethylpiperidin-4-yl group.

9. A compound according to any one of claims 1 to 8 wherein R_t is hydrogen.

10. A compound according to any one of claims 1 to 9 wherein R_3 is methoxy or ethoxy.

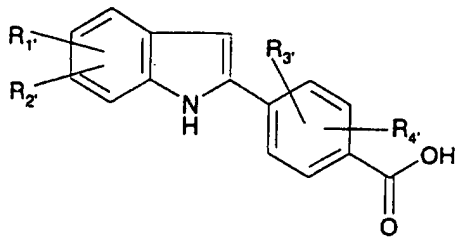
11. A compound according to claim 10 wherein R_3 is located meta to the $-COR_5$ moiety.

12. A compound according to any one of claims 1 11 wherein R_4 is hydrogen or methoxy.

13. A compound according to claim 12 wherein the R_4 group is located meta to the $-COR_5$ moiety.

14. A compound according to any one of claims 1 to 13 selected from
4-(5,6-dichloro-1H-indol-2-yl)-N-[3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl]-3-methoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-[3-[4-(2-pyrimidyl)piperazin-1-yl]propyl]-3-methoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-methoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(3-pyridyl)-3-ethoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(3-(6-methoxypyridyl))-3-ethoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(1-benzylpiperidin-4-yl)-3-ethoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-2,5-dimethoxybenzamide;
4-(5,6-dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,5-dimethoxybenzamide;
4-(5-methoxy-6-chloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide, and;
4-(5-methoxy-6-chloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-methoxybenzamide;
or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof.

15. A process for the preparation of a compound of formula (I) or a salt thereof or a solvate thereof, which process comprises the amidation of a compound of formula (II)



(II)

wherein R_1', R_2', R_3', and R_4' each respectively represent R_1, R_2, R_3, and R_4 as defined in relation to formula (I) or a protected form thereof, with a compound of formula (III)

$$HNR_s'R_t' \qquad \text{(III)}$$

wherein R_s' and R_t' each represent R_s and R_t as defined in relation to formula (I) or a protected form thereof and thereafter, as necessary, carrying out one or more of the following steps:

(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

16. A pharmaceutical composition comprising a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

17. A method for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals which method comprises the administration of an effective non-toxic amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.

18. A method for the treatment of osteoporosis and related osteopenic diseases in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

19. A method for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

20. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

21. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

22. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of osteoporosis and related osteopenic diseases.

23. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for use in the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by

Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal

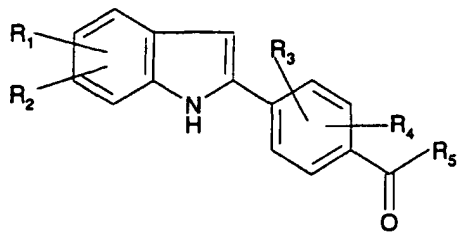
24. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

25. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of osteoporosis and related osteopenic diseases.

26. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia., viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

Abstract

A compound of formula (I)



(I)

or a salt thereof, or a solvate thereof, a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use of the compound or composition in medicine wherein;

R_1 and R_2 each independently represents methoxy or chloro;

R_3 and R_4 each independently represents hydrogen or alkoxy, and;

R_5 represents $-NR_sR_t$ wherein R_s and R_t each independently represent hydrogen, unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.